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(54) Title: MEIOSIS REGULATING COMPOUNDS

(57) Abstract

Certain sterol derivatives, structurally related to natural compounds which can be extracted i.e. from bull testes and from human follicular fluid, can be used for regulating the meiosis in oocytes and in male germ cells.

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MEIOSIS REGULATING COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to pharmacologically active compounds and to their use as medicaments. More particularly it has been found that the sterol derivatives of the invention can be used for regulating the meiosis.

BACKGROUND OF THE INVENTION

Meiosis is the unique and ultimate event of germ cells on which sexual reproduction is based. Meiosis comprises two meiotic divisions. During the first division, exchange between maternal and paternal genes take place before the pairs of chromosomes are separated into the two daughter cells. These contain only half the number (1n) of chromosomes and 2c DNA. The second meiotic division proceeds without a DNA synthesis. This division therefore results in the formation of the haploid germ cells with only 1c DNA.

The meiotic events are similar in the male and female germ cells, but the time schedule and the differentiation processes which lead to ova and to spermatozoa differ profoundly. All female germ cells enter the prophase of the first meiotic division early in life, often before birth, but all are arrested as oocytes later in the prophase (dictyate state) until ovulation after puberty. Thus, from early life the female has a stock of oocytes which is drawn upon until the stock is exhausted. Meiosis in females is not completed until after fertilization, and results in only one ovum and two abortive polar bodies per germ cell. In contrast, only some of the male germ cells enter meiosis from puberty and leave a stem population of germ cells throughout life. Once initiated, meiosis in the male cell proceeds without significant delay and produces 4 spermatozoa.

Only little is known about the mechanisms which control the initiation of meiosis in the male and in the female. In the oocyte, new studies indicate that follicular purines, hypoxanthine or adenosine, could be responsible for meiotic arrest (Downs, SM *et al. Dev Biol* 82 (1985) 454-458; Eppig, JJ *et al. Dev Biol* 119 (1986) 313-321; and Downs, SM *Mol Reprod Dev* 35 (1993) 82-94). The presence of a diffusible meiosis regulating substance was first described by Byskov et al. in a culture system of fetal mouse gonads (Byskov, AG *et al. Dev Biol* 52 (1976) 193-200). A meiosis activating substance (MAS) was secreted by the fetal mouse ovary in which meiosis was ongoing, and a meiosis preventing substance (MPS) was released from the morphologically differentiated testis with resting, non-meiotic germ cells. It was suggested that the relative concentrations of MAS and MPS regulated the beginning, arrest and resumption of meiosis in the male and in the female germ cells (Byskov, AG *et al.* in *The Physiology of Reproduction* (eds. Knobil, E and Neill, JD, Raven Press, New York (1994)). Clearly, if meiosis can be regulated, reproduction can be controlled. A recent article (Byskov, AG *et al. Nature* 374 (1995) 559-562) describes the isolation from bull testes and from human follicular fluid of certain sterols that activate oocyte meiosis. Unfortunately, these sterols are rather labile and utilization of the interesting finding would thus be greatly facilitated if more stable meiosis activating compounds were available.

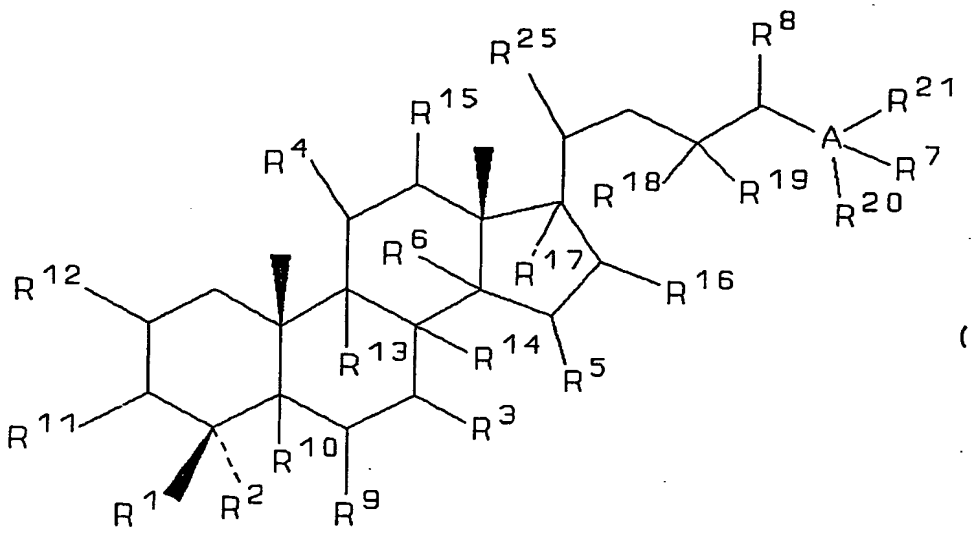
SUMMARY OF THE INVENTION

It is a purpose of the present invention to provide compounds and methods useful for relieving infertility in females and males, particularly in mammals, more particularly in humans.

It is a further purpose of the present invention to provide compounds and methods useful as contraceptives in females and males, particularly in mammals, more particularly in humans.

According to the present invention there are provided novel, stable compounds with interesting pharmacological properties. In particular, the compounds of the invention are useful for regulating the meiosis in oocytes and in male germ cells.

In its broadest aspect, the present invention relates to compounds of the general formula (I)



(I)

wherein R^1 and R^2, independently, are selected from the group comprising hydrogen and branched or unbranched C_1-C_6 alkyl which may be substituted by halogen, hydroxy or cyano, or wherein R^1 and R^2 together designate methylene or, together with the carbon atom to which they are bound, form a cyclopropane ring, a cyclopentane ring, or a cyclohexane ring; R^3 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{26}$ wherein R^{26} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^3 designates, together with R^9 or R^{14}, an additional bond between the carbon atoms to which R^3 and R^9 or R^{14} are bound; R^4 is selected from

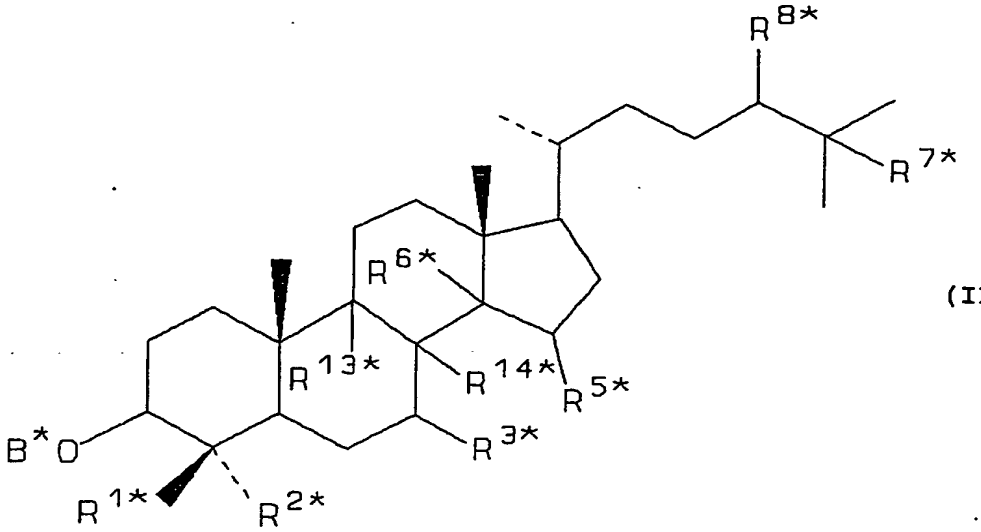
the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, =NOR^{27} wherein R^{27} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^4 designates, together with R^{13} or R^{15}, an additional bond between the carbon atoms to which R^4 and R^{13} or R^{15} are bound; R^5 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, oxo, and =NOR^{22} wherein R^{22} is hydrogen or C_1-C_3 alkyl, or R^5 designates, together with R^6, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^6 is hydrogen or R^6 designates, together with R^5, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^9 is hydrogen or R^9 designates, together with R^3 or R^{10}, an additional bond between the carbon atoms to which R^9 and R^3 or R^{10} are bound; R^{10} is hydrogen or R^{10} designates, together with R^9, an additional bond between the carbon atoms to which R^{10} and R^9 are bound; R^{11} is selected from the group comprising hydroxy, alkoxy, substituted alkoxy, acyloxy, sulphonyloxy, phosphonyloxy, oxo, =NOR^{28} wherein R^{28} is hydrogen or C_1-C_3 alkyl, halogen and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^{11} designates, together with R^{12}, an additional bond between the carbon atoms to which R^{11} and R^{12} are bound; R^{12} is selected from the group comprising hydrogen, C_1-C_3 alkyl, vinyl, C_1-C_3 alkoxy and halogen, or R^{12} designates, together with R^{11}, an additional bond between the carbon atoms to which R^{12} and R^{11} are bound; R^{13} is hydrogen or R^{13} designates, together with R^4 or R^{14}, an additional bond between the carbon atoms to which R^{13} and R^4 or R^{14} are bound; R^{14} is hydrogen or R^{14} designates, together with R^3, R^6 or R^{13}, an additional bond between the carbon atoms to which R^{14} and R^3 or R^6 or R^{13} are bound; R^{15} is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, acetoxy, oxo, and =NOR^{23} wherein R^{23} is hydrogen or C_1-C_3 alkyl, or R^{15} designates, together with R^4, an additional bond between the carbon atoms to which R^{15} and R^4 are bound; R^{16} is selected from the group comprising hydrogen, C_1-C_3 alkyl, methylene, hydroxy, methoxy, oxo and =NOR^{24} wherein R^{24}

is hydrogen or C_1-C_3 alkyl, or R^{16} designates, together with R^{17}, an additional bond between the carbon atoms to which R^{16} and R^{17} are bound; R^{17} is hydrogen or R^{17} designates, together with R^{16}, an additional bond between the carbon atoms to which R^{17} and R^{16} are bound; R^{18} and R^{19} are independently hydrogen or fluoro; R^{25} is selected from the group comprising C_{1-4} alkyl, methylene, hydroxy and oxo; A is a carbon atom or a nitrogen atom; when A is a carbon atom, R^7 is selected from the group comprising hydrogen, hydroxy and fluoro, and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene and halogen, or R^7 designates, together with R^8, an additional bond between the carbon atoms to which R^7 and R^8 are bound; R^{20} is selected from the group comprising C_1-C_4 alkyl, trifluoromethyl and C_3-C_6 cycloalkyl and R^{21} is selected from the group comprising C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl containing up to three halogen atoms, methoxymethyl, acetoxymethyl, and C_3-C_6 cycloalkyl, or R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring; and when A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl and oxo; R^{20} and R^{21} are, independently, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; with the proviso that the compound of the general formula (I) does not have any cumulated double bonds and with the further proviso that the compound is not one of the following compounds:

Cholest-7-ene-3ß-ol;
4-Methylcholest-7-ene-3ß-ol;
4-Ethylcholest-7-ene-3ß-ol;
4,4-Dimethylcholest-7-ene-3ß-ol;
4α-Methyl-4ß-ethylcholest-7-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-7-ene-3ß-ol;
4,4-Diethylcholest-7-ene-3ß-ol;
4-Propylcholest-7-ene-3ß-ol;
4-Butylcholest-7-ene-3ß-ol;
4-Isobutylcholest-7-ene-3ß-ol;

4,4-Tetramethylenecholest-7-ene-3β-ol;
4,4-Pentamethylenecholest-7-ene-3β-ol;
Cholest-8-ene-3β-ol;
4-Methylcholest-8-ene-3β-ol;
4-Ethylcholest-8-ene-3β-ol;
4,4-Dimethylcholest-8-ene-3β-ol;
4α-Methyl-4β-ethylcholest-8-ene-3β-ol;
4α-Ethyl-4β-methylcholest-8-ene-3β-ol;
4,4-Diethylcholest-8-ene-3β-ol;
4-Propylcholest-8-ene-3β-ol;
4-Butylcholest-8-ene-3β-ol;
4-Isobutylcholest-8-ene-3β-ol;
4,4-Tetramethylenecholest-8-ene-3β-ol;
4,4-Pentamethylenecholest-8-ene-3β-ol;
Cholest-8(14)-ene-3β-ol;
4-Methylcholest-8(14)-ene-3β-ol;
4-Ethylcholest-8(14)-ene-3β-ol;
4,4-Dimethylcholest-8(14)-ene-3-ol;
4α-Methyl-4β-ethylcholest-8(14)-ene-3β-ol;
4α-Ethyl-4β-methylcholest-8(14)-ene-3β-ol;
4,4-Diethylcholest-8(14)-ene-3β-ol;
4-Propylcholest-8(14)-ene-3β-ol;
4-Butylcholest-8(14)-ene-3β-ol;
4-Isobutylcholest-8(14)-ene-3β-ol;
4,4-Tetramethylenecholest-8(14)-ene-3β-ol;
4,4-Pentamethylenecholest-8(14)-ene-3β-ol;
Cholesta-8,14-diene-3β-ol;
4-Methylcholesta-8,14-diene-3β-ol;
4-Ethylcholesta-8,14-diene-3β-ol;
4,4-Dimethylcholesta-8,14-diene-3β-ol;
4α-Methyl-4β-ethylcholesta-8,14-diene-3β-ol;
4α-Ethyl-4β-methylcholesta-8,14-diene-3β-ol;
4,4-Diethylcholesta-8,14-diene-3β-ol;
4-Propylcholesta-8,14-diene-3β-ol;
4-Butylcholesta-8,14-diene-3β-ol;
4-Isobutylcholesta-8,14-diene-3β-ol;
4,4-Tetramethylenecholesta-8,14-diene-3β-ol;

4,4-Pentamethylenecholesta-8,14-diene-3ß-ol;
Cholesta-8,24-diene-3ß-ol;
4-Methylcholesta-8,24-diene-3ß-ol;
4-Ethylcholesta-8,24-diene-3ß-ol;
4,4-Dimethylcholesta-8,24-diene-3ß-ol;
4α-Methyl-4ß-ethylcholesta-8,24-diene-3ß-ol;
4α-Ethyl-4ß-methylcholesta-8,24-diene-3ß-ol;
4,4-Diethylcholesta-8,24-diene-3ß-ol;
4-Propylcholesta-8,24-diene-3ß-ol;
4-Butylcholesta-8,24-diene-3ß-ol;
4-Isobutylcholesta-8,24-diene-3ß-ol;
4,4-Tetramethylenecholesta-8,24-diene-3ß-ol;
4,4-Pentamethylenecholesta-8,24-diene-3ß-ol;
Cholesta-8,14,24-triene-3ß-ol;
4-Methylcholesta-8,14,24-triene-3ß-ol;
4-Ethylcholesta-8,14,24-triene-3ß-ol;
4,4-Dimethylcholesta-8,14,24-triene-3ß-ol;
4α-Methyl-4ß-ethylcholesta-8,14,24-triene-3ß-ol;
4α-Ethyl-4ß-methylcholesta-8,14,24-triene-3ß-ol;
4,4-Diethylcholesta-8,14,24-triene-3ß-ol;
4-Propylcholesta-8,14,24-triene-3ß-ol;
4-Butylcholesta-8,14,24-triene-3ß-ol;
4-Isobutylcholesta-8,14,24-triene-3ß-ol;
4,4-Tetramethylenecholesta-8,14,24-triene-3ß-ol; and
4,4-Pentamethylenecholesta-8,14,24-triene-3ß-ol;
and esters and ethers thereof, and with the still further proviso that the compound of the general formula (I) is not a compound of the general formula (II)



(II)

wherein R^{1*} and R^{2*}, independently, are selected from the group comprising hydrogen, branched or unbranched C_1-C_6 alkyl which may be substituted by halogen or hydroxy or wherein R^{1*} and R^{2*}, together with the carbon atom to which they are bound, form a cyclopentane ring or a cyclohexane ring; R^{13*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{3*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{3*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{6*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*}, R^{3*} and R^{5*} are all hydrogen; R^{8*} and R^{7*} are hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; and B^* is either hydrogen or an acyl group, including a sulphonyl group or a phosphonyl group, or a group which together with the remaining part of the molecule forms an

ether.

In a preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 are both hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein one of R^1 and R^2 is hydrogen while the other is methyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 are both methyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^2 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 together designate methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopropane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopentane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclohexane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is $=NOR^{26}$, wherein R^{26} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3, together with R^9, designates an additional bond between the carbon atoms to which R^3 and R^9 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3, together with R^{14}, designates an additional bond between the carbon atoms to which R^3 and R^{14}

are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is $=NOR^{27}$, wherein R^{27} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4, together with R^{13}, designates an additional bond between the carbon atoms to which R^4 and R^{13} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4, together with R^{15}, designates an additional bond between the carbon atoms to which R^4 and R^{15} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is $=NOR^{22}$, wherein R^{22} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5, together with R^6, designates an additional bond between the carbon atoms to which R^5 and R^6 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^6 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^6, together with R^{14}, designates an additional bond between the carbon atoms to which R^6 and R^{14}

are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^9 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^9, together with R^{10}, designates an additional bond between the carbon atoms to which R^9 and R^{10} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{10} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is alkoxy, aralkyloxy, alkoxyalkoxy or alkanoyloxyalkyl, each group comprising a total of up to 10 carbon atoms, preferably up to 8 carbon atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is C_1-C_4 alkoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is ethoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is CH_3OCH_2O-.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is pivaloyloxymethoxy.

In another preferred embodiment, the compound of formula (I)

above is a compound wherein R11 is an acyloxy group derived from an acid having from 1 to 20 carbon atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is an acyloxy group selected from the group comprising acetoxy, benzoyloxy, pivaloyloxy, butyryloxy, nicotinoyloxy, isonicotinoyloxy, hemi succinoyloxy, hemi glutaroyloxy, butylcarbamoyloxy, phenylcarbamoyloxy, butoxycarbonyloxy, tert-butoxycarbonyloxy and ethoxycarbonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is sulphonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is phosphonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is $=NOR^{28}$, wherein R^{28} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11}, together with R^{12}, designates an additional bond between the carbon atoms to which R^{11} and

R^{12} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is C_1-C_3 alkoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{13} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{13}, together with R^{14}, designates an additional bond between the carbon atoms to which R^{13} and R^{14} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{14} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is $=NOR^{23}$, wherein R^{23} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is $=NOR^{24}$, wherein R^{24} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16}, together with R^{17}, designates an additional bond between the carbon atoms to which R^{16} and R^{17} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{17} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{17} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{18} and R^{19} are both hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{18} and R^{19} are both fluoro.

In another preferred embodiment, the compound of formula (I) above is a compound wherein one of R^{18} and R^{19} is fluoro and the other is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is oxo.

In another preferred embodiment, the compound of formula (I)

above is a compound wherein A is a carbon atom.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^7 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7 is fluoro.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7, together with R^8, designates an additional bond between the carbon atoms to which R^7 and R^8 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is trifluoromethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is C_3-C_6 cycloalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 hydroxyalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 haloalkyl containing up to three halogen atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is acetoxymethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is methoxymethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^{21} is C_3-C_6 cycloalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring, preferably a cyclopropyl ring, a cyclopentyl ring or a cyclohexyl ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen and R^7 designates a lone pair of electrons.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^{20} and R^{21}, independently, are selected from the group comprising C_1-C_4 alkyl, cyclopropyl, cyclopentyl and cyclohexyl.

In a further preferred aspect, the present invention relates to the use of a compound of formula (I) above as a medicament, in particular as a medicament for use in the regulation of meiosis. The compound may be used neat or in the form of a liquid or solid composition containing auxiliary ingredients conventionally used in the art.

In the present context, the expression "regulating the meiosis" is used to indicate that certain of the compounds of the invention can be used for stimulating the meiosis *in vitro*, *in vivo*, or *ex vivo*. Thus, the compounds which may be agonists of a naturally occurring meiosis activating substance, can be used in the treatment of infertility which is due to insufficient stimulation of meiosis in females and in males. Other compounds of the invention, which may be antagonists of a naturally occurring meiosis activating substance, can be used for regulating the meiosis, preferably *in vivo*, in a way which makes them suited as contraceptives. In this case the "regulation" means partial or total inhibition.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the regulation of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the stimulation of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the inhibition of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the regulation of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the stimulation of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the inhibition of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a yet still further preferred aspect, the present invention relates to a method of regulating the meiosis in a mammalian germ cell which method comprises administering an effective amount of a compound of formula (I) above to a germ cell in

need of such a treatment.

In a still further aspect, the present invention relates to a method of regulating the meiosis in a mammalian germ cell wherein a compound of formula (I) above is administered to the germ cell by administering the compound to a mammal hosting said cell.

In a still further aspect, the present invention relates to a method wherein the germ cell the meiosis of which is to be regulated by means of a compound of formula (I) above is an oocyte.

In a still further aspect, the present invention relates to a method of regulating the meiosis in an oocyte wherein a compound of formula (I) above is administered to the oocyte *ex vivo*.

In a still further aspect, the present invention relates to a method of regulating the meiosis of a male germ cell by administering a compound of formula (I) above to the cell.

In a still further aspect, the present invention relates to a method whereby mature male germ cells are produced by administering *in vitro* a compound of formula (I) above to testicular tissue containing immature cells.

DETAILED DESCRIPTION OF THE INVENTION

As used in the present description and claims, the expression C_1-C_3 alkyl designates an alkyl group having from one to three carbon atoms; preferred examples are methyl, ethyl and propyl, more preferred methyl and ethyl. Similarly, the expression C_1-C_4 alkyl designates an alkyl group having from one to four carbon atoms; preferred examples are methyl, ethyl, propyl, isopropyl and butyl, more preferred methyl and ethyl. The

expression C_1-C_6 alkyl designates an alkyl group having from one to six carbon atoms; preferred examples are methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl and hexyl, more preferred methyl, ethyl, propyl, isopropyl, butyl and *tert*-butyl, still more preferred methyl and ethyl.

As used in the present description and claims, the expression C_1-C_3 alkoxy designates an alkoxy group having from one to three carbon atoms; preferred examples are methoxy, ethoxy and propoxy, more preferred methoxy and ethoxy.

As used in the present description and claims, the expression halogen preferably designates fluoro and chloro, more preferred fluoro.

The compounds of claim 1 have a number of chiral centres in the molecule and thus exists in several isomeric forms. All these isomeric forms and mixtures thereof are within the scope of the invention.

The compounds of the present invention will influence the meiosis in oocytes as well as in male germ cells.

The existence of a meiosis inducing substance in nature has been known for some time. However, until recently the identity of the meiosis inducing substance or substances was unknown.

The prospects of being able to influence the meiosis are several. According to a preferred embodiment of the present invention, the compounds of claim 1 are used to stimulate the meiosis. According to another preferred embodiment of the present invention, the compounds of claim 1 are used to stimulate the meiosis in humans. Thus, the compounds of claim 1 are promising as new fertility regulating agents without the usual side effect on the somatic cells which are known from the hitherto used hormonal contraceptives which are based on

estrogens and/or gestagens.

For use as a contraceptive agent in females, a meiosis inducing substance can be administered so as to prematurely induce resumption of meiosis in oocytes while they are still in the growing follicle, before the ovulatory peak of gonadotropins occurs. In women, the resumption of the meiosis can, for example, be induced a week after the preceding menstruation has ceased. When ovulated, the resulting overmature oocytes are then most likely not to be fertilized. The normal menstrual cycle is not likely to be affected. In this connection it is important to notice, that the biosynthesis of progesterone in cultured human granulosa cells (somatic cells of the follicle) is not affected by the presence of a meiosis inducing substance whereas the estrogens and gestagens used in the hitherto used hormonal contraceptives do have an adverse effect on the biosynthesis of progesterone.

According to another aspect of this invention, a meiosis inducing substance of claim 1 can be used in the treatment of certain cases of infertility in females, including women, by administration thereof to females who, due to an insufficient own production of meiosis activating substance, are unable to produce mature oocytes. Also, when *in vitro* fertilization is performed, better results are achieved, when a compound of claim 1 is added to the medium in which the oocytes are kept.

When infertility in males, including men, is caused by an insufficient own production of the meiosis activating substance and thus a lack of mature sperm cells, administration of a compound of claim 1 may relieve the problem.

As an alternative to the method described above, contraception in females can also be achieved by administration of a compound of claim 1 which inhibits the meiosis, so that no mature oocytes are produced. Similarly, contraception in males can be achieved by administration of a compound of claim 1 which

inhibits the meiosis, so that no mature sperm cells are produced.

The route of administration of compositions containing a compound of claim 1 may be any route which effectively transports the active compound to its site of action.

Thus, when the compounds of this invention are to be administered to a mammal, they are conveniently provided in the form of a pharmaceutical composition which comprises at least one compound of claim 1 in connection with a pharmaceutically acceptable carrier. For oral use, such compositions are preferably in the form of capsules or tablets.

From the above it will be understood that administrative regimen called for will depend on the condition to be treated. Thus, when used in the treatment of infertility the administration may have to take place once only, or for a limited period, e.g. until pregnancy is achieved. When used as a contraceptive, the compound of claim 1 will either have to be administered continuously or cyclically. When used as a contraceptive by females and not taken continuously, the timing of the administration relative to the ovulation will be important.

Pharmaceutical compositions comprising a compound of claim 1 may further comprise carriers, diluents, absorption enhancers, preservatives, buffers, agents for adjusting the osmotic pressure, tablet disintegrating agents and other ingredients which are conventionally used in the art. Examples of solid carriers are magnesium carbonate, magnesium stearate, dextrin, lactose, sugar, talc, gelatin, pectin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes and cocoa butter.

Liquid compositions include sterile solutions, suspensions and emulsions. Such liquid compositions may be suitable for

injection or for use in connection with *ex vivo* and *in vitro* fertilization. The liquid compositions may contain other ingredients which are conventionally used in the art, some of which are mentioned in the list above.

Further, a composition for transdermal administration of a compound of this invention may be provided in the form of a patch and a composition for nasal administration may be provided in the form of a nasal spray in liquid or powder form.

The dose of a compound of the invention to be used will be determined by a physician and will depend, *inter alia*, on the particular compound employed, on the route of administration and on the purpose of the use.

The compounds of claim 1 can be synthesized by methods known per se.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

EXAMPLE 1

Preparation of 7-oxo-5α-cholest-8-ene-3β-ol.

0.50 g of 3β-acetoxy-7-oxo-5α-cholest-8-ene (Fieser, LF *J Am Chem Soc* (1953) 4395) was refluxed in a mixture of 30 ml of ethanol and 20 ml of 1M aqueous sodium hydroxide for 1 hour. After cooling to room temperature, 23 ml of 1M hydrochloric acid and 100 ml of water were added. After cooling on an ice

bath, the precipitate was filtered off, washed with water and dried to give 0.435 g of the crude compound which was purified by chromatography on silica gel (methylene chloride/methanol, 40:1 (w/w)) and crystallized from methanol/water to give 0.198 g of the title compound.

Melting point: 115-117° C.
The ^{1}H-NMR spectrum ($CDCl_3$,δ) showed characteristic signals at: 0.59 (s,3H); 1.18 (s,3H); 3.64 (m,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 69.5; 132.8; 164.8; 198.6.

EXAMPLE 2
Preparation of 7-oxo-5α-cholesta-8.14-diene-3β-ol.

The compound was prepared as described by Fieser, LF *et al. J Am Chem Soc* (1953) 4719) and showed the following characteristic physical constants:

Melting point: 140-142° C.
^{1}H-NMR spectrum ($CDCl_3$,δ): 0.79 (s,3H), 1.14 (s,3H), 3.66 (m,1H), 6.45 (s,1H).
^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz): 69.4; 126.1; 126.6; 140.8; 164.9; 197.2.

EXAMPLE 3
Preparation of 7α-methyl-5α-cholest-8-ene-3β,7β-diol.

0.50 g of 3β-acetoxy-7-oxo-5α-cholest-8-ene (Fieser, LF *J Am Chem Soc* (1953) 4395) was dissolved in 10 ml of tetrahydrofuran and 3 ml of 3M methylmagnesium chloride in tetrahydrofuran was added dropwise at 0° C over 15 minutes. The mixture was stirred at room temperature for 1 hour, cooled to 0° C, and 50 ml of a

1M solution of ammonium chloride was added dropwise over 5 minutes. The mixture was extracted twice with 50 ml of ethylacetate. The combined organic phases were washed with water and brine and evaporated to yield 474 mg of the crude product which was crystallized from ethylacetate/heptane to yield 168 mg of the title compound.

Melting point: 92-94° C.
The ^{1}H-NMR spectrum ($CDCl_3$, δ) showed characteristic signals at: 0.69 (s,3H), 1.03 (s,3H), 1.37 (s,3H), 3.62 (m,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 50.3 MHz) showed characteristic signals at: 70.7; 73.8; 132.9; 139.2.

From the mother liquor another crop (107 mg) of the title compound was isolated.

EXAMPLE 4

Preparation of 11-oxo-5α-cholest-8-ene-3β-ol.

This compound was prepared as described by Parish, ES *et al.* *Steroids* 48 (1986) 407) and showed physical constants as described in the literature.

EXAMPLE 5

Preparation of 3β-Hydroxy-5α-cholest-8-ene-7-oxime.

0.25 g of 7-oxo-5α-cholest-8-ene-3β-ol (cf. Example 1) was dissolved in 10 ml of dry pyridine. 0.43 g of hydroxylamine hydrochloride was added, and the mixture was stirred at 70° C for 3 hours. After evaporation to dryness, the residue was triturated with water to give 238 mg of the crude product. Recrystallisation from methanol yielded 164 mg of the title compound.

Melting point: 218-223° C.

The ^{1}H-NMR spectrum ($CDCl_3$,δ) showed characteristic signals at: 0.62 (s,3H), 1.03 (s,3H), 3.0 (dd,1H), 3.62 (m,1H), 7.52 (broad s,1H).

The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 69.9, 126.7, 149.8, 157.7.

EXAMPLE 6

Preparation of 3β-acetoxy-7-oxo-5α-cholest-8-ene.

This compound was prepared as described by Fieser, LF *J Am Chem Soc* (1953) 4395 and showed physical constants as described in the literature.

EXAMPLE 7

Preparation of 3β-acetoxy-7-oxo-5α-cholesta-8,14-diene.

This compound was prepared as described by Fieser, LF *et al. J Am Chem Soc* (1953) 4719 and showed physical constants as described in the literature.

EXAMPLE 8

Preparation of 7-oxo-5α-cholest-8-ene-3β-yl benzoate.

This compound was prepared as described by Parish EJ *et al. Steroids* 48 (1986) 407 and showed physical constants as described in the literature.

EXAMPLE 9

Preparation of 7-methylene-5α-cholest-9-ene-3β-ol.

0.54 g of sodium hydride (60%) was dissolved in 10 ml of dimethyl sulfoxide at 70° C. After 15 minutes a solution of 5.24 g of methyltriphenylphosphonium bromide in 33 ml of dimethyl sulfoxide and then a solution of 3β-acetoxy-7-oxo-5α-cholest-8-ene (cf. Example 6) in 28 ml benzene was added. The mixture was stirred at 60° C for 22 hours, cooled to room temperature, poured on 1M hydrochloride acid/ice, and extracted several times with benzene. The combined organic phases were evaporated to dryness and the residue was dissolved in a mixture of methanol/water/cyclohexane, 13:7:20 (w/w). The methanol/water phase was extracted several times with cyclohexane and the combined cyclohexane phases were evaporated to dryness to give 1.32 g of an oil which was dissolved in 15 ml of heptane, filtered and evaporated to dryness. The residue (0.80 g) was chromatographed on 40 g silica gel (toluene/ethylacetate, 9:1 (w/w)) to give 247 mg of an almost pure product, which was crystallized from methanol to yield 110 mg of the title compound.

Melting point: 44-50° C.

The ^{1}H-NMR spectrum ($CDCl_3$, δ) showed characteristic signals at: 0.65 (s,3H); 1.06 (s,3H); 2.62 (d,1H); 3.58 (m,1H); 4.68 (d,2H); 5.27 (d,1H).

The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 70.5; 105.2; 115.7; 146.1; 150.5.

EXAMPLE 10

Preparation of 7-methyl-5α-cholesta-6,8-diene-3β-ol.

0.90 g of 7α-methyl-5α-cholest-8-ene-3β,7β-diol (cf. Example 3) was suspended in 55 ml of formic acid and stirred overnight at

room temperature. The mixture was poured on ice water and the precipitated compound was filtered off, washed with water, and dried. The residue (0.84 g) was refluxed in a mixture of 50 ml ethanol and 25 ml 1M aqueous sodium carbonate for 15 minutes. The solvent was evaporated and the residue was redissolved in methylene chloride and water. The organic phase was evaporated to dryness and crystallized from ethanol/water to yield 395 mg of the title compound.

Melting point: 112-113° C.

The ^{1}H-NMR spectrum ($CDCl_3$, δ) of the product showed characteristic signals at: 0.58 (s,3H), 0.88 (s,3H), 1.83 (s.3H), 3.58 (m,1H), 5.37 (d,1H).

The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 70.9, 116.6, 129.0, 129.6, 145.3.

EXAMPLE 11

Preparation of 11-oxo-5α-cholest-8-ene-3β-yl benzoate.

This compound was prepared as described by Parish, EJ *et al. Steroids* 48 (1986) 407) and showed physical constants as described in literature.

EXAMPLE 12

Preparation of cholesta-8,14-diene-5α-H-3-one.

Cholesta-8,14-diene-5α-3-one was prepared according to Dolle *J Org Chem* 51 (1986) 4047-4053. The product showed the following physical characteristics:

^{1}H-NMR: Hδ: 5.78 (d 1H, C4H), 5.16 (1H, m, C7H)

Elementary analysis:

Cal: C: 84.7; H: 11.1; O: 4.18

Found: C: 84.7; H: 11.4.

EXAMPLE 13

Preparation of 3α-flourocholesta-8,14-diene.

Cholesta-8,14-diene-3ß-ol (1.17 g, 3 mmol) was dissolved in 10 ml of methylenechloride and cooled to -78° C. Over 10 min a solution of diethylaminosulfur trifluoride (1.4 g, 8.7 mmol) in 10 ml of methylenechloride was added at -78° C. The mixture was stirred for 1 1/2 hour at -78° C and was then slowly heated to room temperature. To the reaction mixture was added 15 ml of water while stirring was continued. The organic phase was separated and washed with 30 ml of 5% $NaHCO_3$ and then with water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography using heptane for a first fraction and heptane/acetone, 95:5 (w/w) for a second fraction containing 3α-fluorocholesta-8,14 diene, 0.14 g (12%).

Melting point: 98.6° C

Elementary analysis:

Cal C: 83.88; H: 11.21; F: 4.91.

Found C: 83.92; H: 11.75.

^{19}F-NMR: δ 181.0 and 181.2 (J_{HCF} 45.2 Hz, C_3-αF).

EXAMPLE 14

Preparation of cholesta-2,8,14-triene.

The title compound was prepared by using a method analogous to a method described in *J Chemical Research* (miniprint) (1979) 4714-4755.

Cholesta-8,14-diene-3ß-ol (1.17 g, 3 mmol) was dissolved in 10 ml of methylenechloride and cooled to -78° C. Over 10 min a solution of diethylaminosulfur trifluoride (1.4 g, 8,7 mmol) in 10 ml of methylenechloride was added at -78° C. The mixture was stirred and was then slowly heated to the room temperature. The

reaction mixture was added 15 ml water while stirring was continued. The organic phase was separated and washed with 30 ml of 5% $NaHCO_3$ and then with water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography using heptane for a first fraction A giving cholesta-2,8,14-triene, 0.23 g.

Melting point: 104.7° C.
Elementary analysis:
Cal C: 88.45; H: 11.55.
Found C: 88.58; H: 11.89.
NMR: Hδ: 5.64 (m 2H; C_2-H; C_3-H)δ 5.35 (s,1H C 15H).
Cδ: 125.95 (C_3), 125.67 (C_2).

EXAMPLE 15

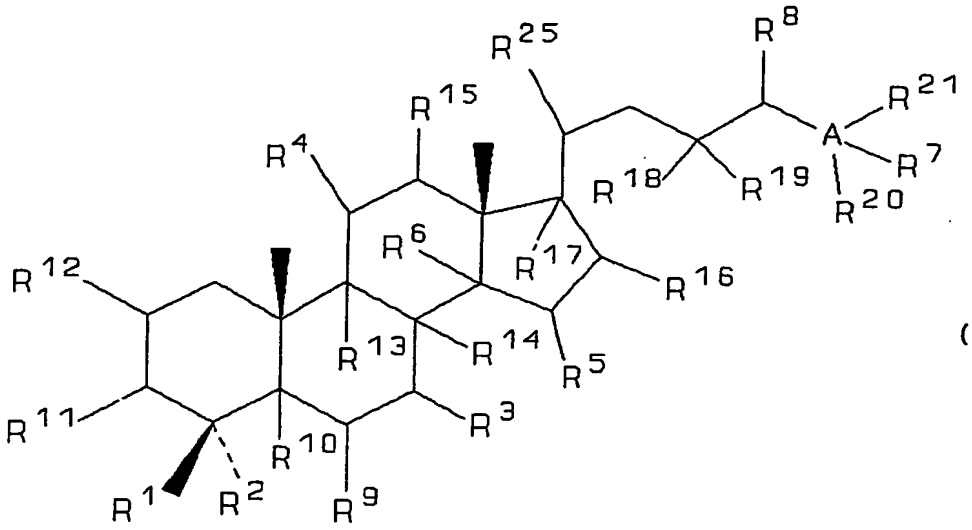
Preparation of cholesta-8,14-diene-5α(H)-3-(E),(Z)-oxime.

Cholesta-8,14-diene-3-one (1.0 g, 2.61 mmol) was dissolved in 15 ml of pyridine and hydroxylamine, HCl (0.29 g, 4.23 mmol) was added. The reaction mixture was heated at 70-72° C for 1 1/2 hour while stirred. The reaction mixture was cooled and evaporated to dryness. 30 ml of 50% acetic acid/water was added and the crystals formed were separated by filtration. The crystals were dissolved in heptane and washed with water. The organic phase was separated and evaporated to dryness. The crystals were recrystallized from ethanol to give 0.91 g of 5α-cholesta-8,14-diene-3-(E) and (Z)-oxime.

Elementary analysis:
Cal C: 81.55; H: 10.90; N: 3.52; O: 4.02.
Found: 81.65; H: 11.30; N: 3.43.
^{13}C-NMR: δ 159,66 and 159.51 (3-C).

CLAIMS

1. A compound of the general formula (I)



(I)

wherein R^1 and R^2, independently, are selected from the group comprising hydrogen and branched or unbranched C_1-C_6 alkyl which may be substituted by halogen, hydroxy or cyano, or wherein R^1 and R^2 together designate methylene or, together with the carbon atom to which they are bound, form a cyclopropane ring, a cyclopentane ring, or a cyclohexane ring; R^3 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{26}$ wherein R^{26} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^3 designates, together with R^9 or R^{14}, an additional bond between the carbon atoms to which R^3 and R^9 or R^{14} are bound; R^4 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{27}$ wherein R^{27} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^4 designates, together with R^{13} or R^{15}, an additional bond between the carbon atoms to which R^4 and R^{13} or R^{15} are bound; R^5 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy,

methoxy, oxo, and =NOR^{22} wherein R^{22} is hydrogen or C_1-C_3 alkyl, or R^5 designates, together with R^6, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^6 is hydrogen or R^6 designates, together with R^5, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^9 is hydrogen or R^9 designates, together with R^3 or R^{10}, an additional bond between the carbon atoms to which R^9 and R^3 or R^{10} are bound; R^{10} is hydrogen or R^{10} designates, together with R^9, an additional bond between the carbon atoms to which R^{10} and R^9 are bound; R^{11} is selected from the group comprising hydroxy, alkoxy, substituted alkoxy, acyloxy, sulphonyloxy, phosphonyloxy, oxo, =NOR^{28} wherein R^{28} is hydrogen or C_1-C_3 alkyl, halogen and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^{11} designates, together with R^{12}, an additional bond between the carbon atoms to which R^{11} and R^{12} are bound; R^{12} is selected from the group comprising hydrogen, C_1-C_3 alkyl, vinyl, C_1-C_3 alkoxy and halogen, or R^{12} designates, together with R^{11}, an additional bond between the carbon atoms to which R^{12} and R^{11} are bound; R^{13} is hydrogen or R^{13} designates, together with R^4 or R^{14}, an additional bond between the carbon atoms to which R^{13} and R^4 or R^{14} are bound; R^{14} is hydrogen or R^{14} designates, together with R^3, R^6 or R^{13}, an additional bond between the carbon atoms to which R^{14} and R^3 or R^6 or R^{13} are bound; R^{15} is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, acetoxy, oxo, and =NOR^{23} wherein R^{23} is hydrogen or C_1-C_3 alkyl, or R^{15} designates, together with R^4, an additional bond between the carbon atoms to which R^{15} and R^4 are bound; R^{16} is selected from the group comprising hydrogen, C_1-C_3 alkyl, methylene, hydroxy, methoxy, oxo and =NOR^{24} wherein R^{24} is hydrogen or C_1-C_3 alkyl, or R^{16} designates, together with R^{17}, an additional bond between the carbon atoms to which R^{16} and R^{17} are bound; R^{17} is hydrogen or hydroxy or R^{17} designates, together with R^{16}, an additional bond between the carbon atoms to which R^{17} and R^{16} are bound; R^{18} and R^{19} are, independently, hydrogen or fluoro; R^{25} is selected from the

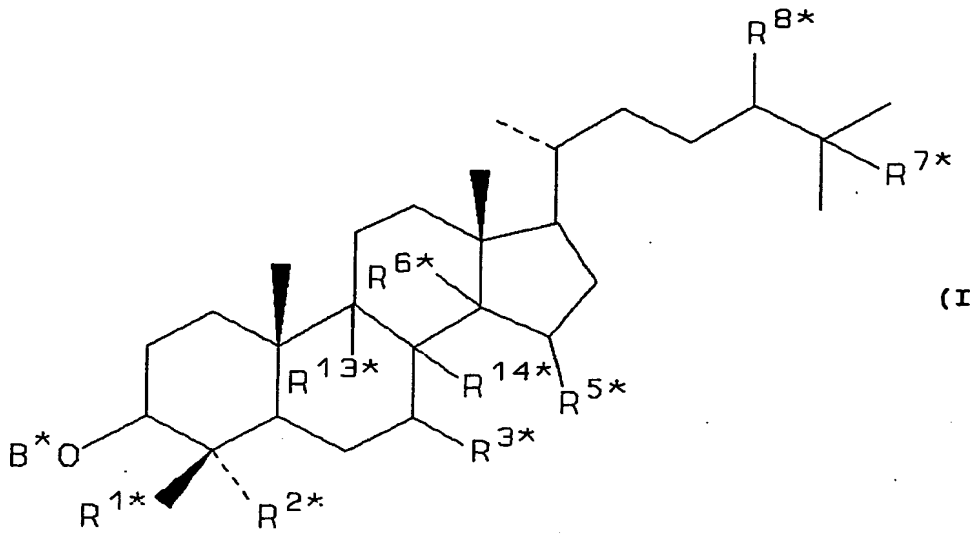
group comprising hydrogen, C_{1-4} alkyl, methylene, hydroxy and oxo; A is a carbon atom or a nitrogen atom; when A is a carbon atom, R^7 is selected from the group comprising hydrogen, hydroxy and fluoro, and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene and halogen, or R^7 designates, together with R^8, an additional bond between the carbon atoms to which R^7 and R^8 are bound; R^{20} is selected from the group comprising C_1-C_4 alkyl, trifluoromethyl and C_3-C_6 cycloalkyl and R^{21} is selected from the group comprising C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl containing up to three halogen atoms, methoxymethyl, acetoxymethyl, and C_3-C_6 cycloalkyl, or R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring; and when A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl and oxo; R^{20} and R^{21} are, independently, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; with the proviso that the compound of the general formula (I) does not have any cumulated double bonds and with the further proviso that the compound is not one of the following compounds:

Cholest-7-ene-3ß-ol;
4-Methylcholest-7-ene-3ß-ol;
4-Ethylcholest-7-ene-3ß-ol;
4,4-Dimethylcholest-7-ene-3ß-ol;
4α-Methyl-4ß-ethylcholest-7-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-7-ene-3ß-ol;
4,4-Diethylcholest-7-ene-3ß-ol;
4-Propylcholest-7-ene-3ß-ol;
4-Butylcholest-7-ene-3ß-ol;
4-Isobutylcholest-7-ene-3ß-ol;
4,4-Tetramethylenecholest-7-ene-3ß-ol;
4,4-Pentamethylenecholest-7-ene-3ß-ol;
Cholest-8-ene-3ß-ol;
4-Methylcholest-8-ene-3ß-ol;
4-Ethylcholest-8-ene-3ß-ol;

4,4-Dimethylcholest-8-ene-3ß-ol;
4α-Methyl-4ß-ethylcholest-8-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-8-ene-3ß-ol;
4,4-Diethylcholest-8-ene-3ß-ol;
4-Propylcholest-8-ene-3ß-ol;
4-Butylcholest-8-ene-3ß-ol;
4-Isobutylcholest-8-ene-3ß-ol;
4,4-Tetramethylenecholest-8-ene-3ß-ol;
4,4-Pentamethylenecholest-8-ene-3ß-ol;
Cholest-8(14)-ene-3ß-ol;
4-Methylcholest-8(14)-ene-3ß-ol;
4-Ethylcholest-8(14)-ene-3ß-ol;
4,4-Dimethylcholest-8(14)-ene-3-ol;
4α-Methyl-4ß-ethylcholest-8(14)-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-8(14)-ene-3ß-ol;
4,4-Diethylcholest-8(14)-ene-3ß-ol;
4-Propylcholest-8(14)-ene-3ß-ol;
4-Butylcholest-8(14)-ene-3ß-ol;
4-Isobutylcholest-8(14)-ene-3ß-ol;
4,4-Tetramethylenecholest-8(14)-ene-3ß-ol;
4,4-Pentamethylenecholest-8(14)-ene-3ß-ol;
Cholesta-8,14-diene-3ß-ol;
4-Methylcholesta-8,14-diene-3ß-ol;
4-Ethylcholesta-8,14-diene-3ß-ol;
4,4-Dimethylcholesta-8,14-diene-3ß-ol;
4α-Methyl-4ß-ethylcholesta-8,14-diene-3ß-ol;
4α-Ethyl-4ß-methylcholesta-8,14-diene-3ß-ol;
4,4-Diethylcholesta-8,14-diene-3ß-ol;
4-Propylcholesta-8,14-diene-3ß-ol;
4-Butylcholesta-8,14-diene-3ß-ol;
4-Isobutylcholesta-8,14-diene-3ß-ol;
4,4-Tetramethylenecholesta-8,14-diene-3ß-ol;
4,4-Pentamethylenecholesta-8,14-diene-3ß-ol;
Cholesta-8,24-diene-3ß-ol;
4-Methylcholesta-8,24-diene-3ß-ol;
4-Ethylcholesta-8,24-diene-3ß-ol;
4,4-Dimethylcholesta-8,24-diene-3ß-ol;

4α-Methyl-4β-ethylcholesta-8,24-diene-3β-ol;
4α-Ethyl-4β-methylcholesta-8,24-diene-3β-ol;
4,4-Diethylcholesta-8,24-diene-3β-ol;
4-Propylcholesta-8,24-diene-3β-ol;
4-Butylcholesta-8,24-diene-3β-ol;
4-Isobutylcholesta-8,24-diene-3β-ol;
4,4-Tetramethylenecholesta-8,24-diene-3β-ol;
4,4-Pentamethylenecholesta-8,24-diene-3β-ol;
Cholesta-8,14,24-triene-3β-ol;
4-Methylcholesta-8,14,24-triene-3β-ol;
4-Ethylcholesta-8,14,24-triene-3β-ol;
4,4-Dimethylcholesta-8,14,24-triene-3β-ol;
4α-Methyl-4β-ethylcholesta-8,14,24-triene-3β-ol;
4α-Ethyl-4β-methylcholesta-8,14,24-triene-3β-ol;
4,4-Diethylcholesta-8,14,24-triene-3β-ol;
4-Propylcholesta-8,14,24-triene-3β-ol;
4-Butylcholesta-8,14,24-triene-3β-ol;
4-Isobutylcholesta-8,14,24-triene-3β-ol;
4,4-Tetramethylenecholesta-8,14,24-triene-3β-ol; and
4,4-Pentamethylenecholesta-8,14,24-triene-3β-ol;
and esters and ethers thereof.

2. A compound according to claim 1 with the proviso that it is not a compound of the general formula (II)



(II)

wherein R^{1*} and R^{2*}, independently, are selected from the group comprising hydrogen, branched or unbranched C_1-C_6 alkyl which may be substituted by halogen or hydroxy or wherein R^{1*} and R^{2*}, together with the carbon atom to which they are bound, form a cyclopentane ring or a cyclohexane ring; R^{13*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{3*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{3*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{6*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*}, R^{3*} and R^{5*} are all hydrogen; R^{8*} and R^{7*} are hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; and B^* is either hydrogen or an acyl group, including a sulphonyl group or a phosphonyl group, or a group which together with the remaining part of the molecule forms an ether.

3. A compound according to claim 1 or 2 wherein R^1 and R^2 are both hydrogen.

4. A compound according to claim 1 or 2 wherein one of R^1 and R^2 is hydrogen while the other is methyl.

5. A compound according to claim 1 or 2 wherein R^1 and R^2 are both methyl.

6. A compound according to claim 1 or 2 wherein R^1 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

7. A compound according to claim 1 or 2 wherein R^2 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

8. A compound according to claim 1 or 2 wherein R^1 and R^2 together designate methylene.

9. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopropane ring.

10. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopentane ring.

11. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclohexane ring.

12. A compound according to any one of the preceding claims wherein R^3 is hydrogen.

13. A compound according to any one of the claims 1 to 11 wherein R^3 is methylene.

14. A compound according to any one of the claims 1 to 11 wherein R^3 is hydroxy.

15. A compound according to any one of the claims 1 to 11 wherein R^3 is methoxy or acetoxy.

16. A compound according to any one of the claims 1 to 11 wherein R^3 is halogen.

17. A compound according to any one of the claims 1 to 11 wherein R^3 is oxo.

18. A compound according to any one of the claims 1 to 11 wherein R^3 is =NOH.

19. A compound according to any one of the claims 1 to 11 wherein R^3 is $=NOR^{26}$, wherein R^{26} is C_1-C_3 alkyl.

20. A compound according to any one of the claims 1 to 11 wherein R^3 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

21. A compound according to any one of the claims 1 to 11 wherein R^3, together with R^9, designates an additional bond between the carbon atoms to which R^3 and R^9 are bound.

22. A compound according to any one of the claims 1 to 11 wherein R^3, together with R^{14}, designates an additional bond between the carbon atoms to which R^3 and R^{14} are bound.

23. A compound according to any one of the claims 1 to 22 wherein R^4 is hydrogen.

24. A compound according to any one of the claims 1 to 22 wherein R^4 is methylene.

25. A compound according to any one of the claims 1 to 22 wherein R^4 is hydroxy.

26. A compound according to any one of the claims 1 to 22 wherein R^4 is methoxy or acetoxy.

27. A compound according to any one of the claims 1 to 22 wherein R^4 is oxo.

28. A compound according to any one of the claims 1 to 22 wherein R^4 is =NOH.

29. A compound according to any one of the claims 1 to 22 wherein R^4 is $=NOR^{27}$, wherein R^{27} is C_1-C_3 alkyl.

30. A compound according to any one of the claims 1 to 22 wherein R^4 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

31. A compound according to any one of the claims 1 to 22 wherein R^4, together with R^{13}, designates an additional bond between the carbon atoms to which R^4 and R^{13} are bound.

32. A compound according to any one of the claims 1 to 22 wherein R^4, together with R^{15}, designates an additional bond between the carbon atoms to which R^4 and R^{15} are bound.

33. A compound according to any one of the claims 1 to 32 wherein R^5 is hydrogen.

34. A compound according to any one of the claims 1 to 32 wherein R^5 is C_1-C_4 alkyl.

35. A compound according to any one of the claims 1 to 32 wherein R^5 is methylene.

36. A compound according to any one of the claims 1 to 32 wherein R^5 is hydroxy.

37. A compound according to any one of the claims 1 to 32 wherein R^5 is methoxy.

38. A compound according to any one of the claims 1 to 32 wherein R^5 is oxo.

39. A compound according to any one of the claims 1 to 32 wherein R^5 is =NOH.

40. A compound according to any one of the claims 1 to 32 wherein R^5 is $=NOR^{22}$, wherein R^{22} is C_1-C_3 alkyl.

41. A compound according to any one of the claims 1 to 32 wherein R^5, together with R^6, designates an additional bond between the carbon atoms to which R^5 and R^6 are bound.

42. A compound according to any one of the claims 1 to 41 wherein R^6 is hydrogen.

43. A compound according to any one of the claims 1 to 42 wherein R^6, together with R^{14}, designates an additional bond between the carbon atoms to which R^6 and R^{14} are bound.

44. A compound according to any one of the claims 1 to 43 wherein R^9 is hydrogen.

45. A compound according to any one of the claims 1 to 37 wherein R^9, together with R^{10}, designates an additional bond between the carbon atoms to which R^9 and R^{10} are bound.

46. A compound according to any one of the claims 1 to 40 wherein R^{10} is hydrogen.

47. A compound according to any one of the claims 1 to 41 wherein R^{11} is hydroxy.

48. A compound according to any one of the claims 1 to 41 wherein R^{11} is alkoxy, aralkyloxy, alkoxyalkoxy or alkanoyloxyalkyl, each group comprising a total of up to 10 carbon atoms, preferably up to 8 carbon atoms.

49. A compound according to any one of the claims 1 to 41 wherein R^{11} is C_1-C_4 alkoxy.

50. A compound according to any one of the claims 1 to 41 wherein R^{11} is methoxy.

51. A compound according to any one of the claims 1 to 41 wherein R^{11} is ethoxy.

52. A compound according to any one of the claims 1 to 41 wherein R^{11} is CH_3OCH_2O-.

53. A compound according to any one of the claims 1 to 41 wherein R^{11} is pivaloyloxymethoxy.

54. A compound according to any one of the claims 1 to 41 wherein R^{11} is an acyloxy group derived from an acid having from 1 to 20 carbon atoms.

55. A compound according to any one of the claims 1 to 41 wherein R^{11} is an acyloxy group selected from the group comprising acetoxy, benzoyloxy, pivaloyloxy, butyryloxy, nicotinoyloxy, isonicotinoyloxy, hemi succinoyloxy, hemi glutaroyloxy, butylcarbamoyloxy, phenylcarbamoyloxy, butoxycarbonyloxy, tert-butoxycarbonyloxy and ethoxycarbonyloxy.

56. A compound according to any one of the claims 1 to 41 wherein R^{11} is sulphonyloxy.

57. A compound according to any one of the claims 1 to 41 wherein R^{11} is phosphonyloxy.

58. A compound according to any one of the claims 1 to 41 wherein R^{11} is oxo.

59. A compound according to any one of the claims 1 to 41 wherein R^{11} is =NOH.

60. A compound according to any one of the claims 1 to 41 wherein R^{11} is $=NOR^{28}$, wherein R^{28} is C_1-C_3 alkyl.

61. A compound according to any one of the claims 1 to 41 wherein R^{11} is halogen.

62. A compound according to any one of the claims 1 to 41 wherein R^{11} is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

63. A compound according to any one of the claims 1 to 41 wherein R^{11}, together with R^{12}, designates an additional bond between the carbon atoms to which R^{11} and R^{12} are bound.

64. A compound according to any one of the claims 1 to 63 wherein R^{12} is hydrogen.

65. A compound according to any one of the claims 1 to 63 wherein R^{12} is C_1-C_3 alkyl.

66. A compound according to any one of the claims 1 to 63 wherein R^{12} is C_1-C_3 alkoxy.

67. A compound according to any one of the claims 1 to 63 wherein R^{12} is halogen.

68. A compound according to any one of the claims 1 to 67 wherein R^{13} is hydrogen.

69. A compound according to any one of the claims 1 to 67 wherein R^{13}, together with R^{14}, designates an additional bond between the carbon atoms to which R^{13} and R^{14} are bound.

70. A compound according to any one of the claims 1 to 68 wherein R^{14} is hydrogen.

71. A compound according to any one of the claims 1 to 70 wherein R^{15} is hydrogen.

72. A compound according to any one of the claims 1 to 70 wherein R^{15} is C_1-C_4 alkyl.

73. A compound according to any one of the claims 1 to 70 wherein R^{15} is methylene.

74. A compound according to any one of the claims 1 to 70 wherein R^{15} is hydroxy.

75. A compound according to any one of the claims 1 to 70 wherein R^{15} is methoxy or acetoxy.

76. A compound according to any one of the claims 1 to 70 wherein R^{15} is oxo.

77. A compound according to any one of the claims 1 to 70 wherein R^{15} is =NOH.

78. A compound according to any one of the claims 1 to 70 wherein R^{15} is $=NOR^{23}$, wherein R^{23} is C_1-C_3 alkyl.

79. A compound according to any one of the claims 1 to 78 wherein R^{16} is hydrogen.

80. A compound according to any one of the claims 1 to 78 wherein R^{16} is C_1-C_3 alkyl.

81. A compound according to any one of the claims 1 to 78 wherein R^{16} is methylene.

82. A compound according to any one of the claims 1 to 78 wherein R^{16} is hydroxy.

83. A compound according to any one of the claims 1 to 78 wherein R^{16} is methoxy.

84. A compound according to any one of the claims 1 to 78 wherein R^{16} is oxo.

85. A compound according to any one of the claims 1 to 78 wherein R^{16} is =NOH.

86. A compound according to any one of the claims 1 to 78 wherein R^{16} is $=NOR^{24}$, wherein R^{24} is C_1-C_3 alkyl.

87. A compound according to any one of the claims 1 to 78 wherein R^{16}, together with R^{17}, designates an additional bond between the carbon atoms to which R^{16} and R^{17} are bound.

88. A compound according to any one of the claims 1 to 87 wherein R^{17} is hydrogen or hydroxy.

89. A compound according to any one of the claims 1 to 88 wherein R^{18} and R^{19} are both hydrogen.

90. A compound according to any one of the claims 1 to 88 wherein R^{18} and R^{19} are both fluoro.

91. A compound according to any one of the claims 1 to 88 wherein one of R^{18} and R^{19} is fluoro and the other is hydrogen.

92. A compound according to any one of the preceding claims wherein R^{25} is hydrogen.

93. A compound according to any one of the preceding claims wherein R^{25} is C_1-C_4 alkyl.

94. A compound according to any one of the claims 1 to 91 wherein R^{25} is methylene.

95. A compound according to any one of the claims 1 to 91 wherein R^{25} is hydroxy.

96. A compound according to any one of the claims 1 to 91 wherein R^{25} is oxo.

97. A compound according to any one of the claims 1 to 96 wherein A is a carbon atom.

98. A compound according to claim 97 wherein R^7 is hydrogen.

99. A compound according to claim 97 wherein R^7 is hydroxy.

100. A compound according to claim 97 wherein R^7 is fluoro.

101. A compound according to claim 97 wherein R^7, together with R^8, designates an additional bond between the carbon atoms to which R^7 and R^8 are bound.

102. A compound according to claim 97 wherein R^8 is hydrogen.

103. A compound according to claim 97 wherein R^8 is C_1-C_4 alkyl.

104. A compound according to claim 97 wherein R^8 is methylene.

105. A compound according to claim 97 wherein R^8 is halogen.

106. A compound according to any one of the claims 1 to 105 wherein R^{20} is C_1-C_4 alkyl.

107. A compound according to any one of the claims 1 to 105 wherein R^{20} is trifluoromethyl.

108. A compound according to any one of the claims 1 to 105 wherein R^{20} is C_3-C_6 cycloalkyl.

109. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 alkyl.

110. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 hydroxyalkyl.

111. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 haloalkyl containing up to three halogen atoms.

112. A compound according to any one of the claims 1 to 108 wherein R^{21} is methoxymethyl or acetoxymethyl.

113. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_3-C_6 cycloalkyl.

114. A compound according to any one of the claims 1 to 105 wherein R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring, preferably a cyclopropyl ring, a cyclopentyl ring or a cyclohexyl ring.

115. A compound according to any one of the claims 1 to 96 wherein A is a nitrogen atom.

116. A compound according to claim 115 wherein R^8 is hydrogen.

117. A compound according to claim 115 wherein R^8 is C_1-C_4 alkyl.

118. A compound according to claim 115 wherein R^8 is oxo.

119. A compound according to claim 115 and any one of the claims 47 to 93 wherein R^{20} and R^{21}, independently, are selected from the group comprising C_1-C_4 alkyl, cyclopropyl, cyclopentyl and cyclohexyl.

120. A compound according to any of the claims 1 to 119 for use as a medicament.

121. A compound of general formula (I) as described in any of the claims 1 to 119 for use in the regulation of meiosis.

122. A method of regulating the meiosis in a mammalian germ cell which method comprises administering an effective amount of a compound according to any one of the claims 1 to 119 to a germ cell in need of such a treatment.

123. A method according to claim 122 wherein a compound according to any one of the claims 1 to 119 is administered to a germ cell by administering it to a mammal hosting said cell.

124. A method according to claim 122 or 123 wherein the germ cell the meiosis of which is to be regulated is an oocyte.

125. A method according to claim 122 wherein a compound according to any one of the claims 1 to 119 is administered to an oocyte ex vivo.

126. A method according to claim 123 wherein the germ cell the meiosis of which is to be regulated is a male germ cell.

127. A method according to claim 122 whereby mature male germ cells are produced by administering a compound according to any one of the claims 1 to 119 to testicular tissue *in vitro*.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00273

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07J 9/00, A61K 31/575
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07J, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, REGISTRY, WPI, US PATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1991:472013, Frelek, Jadwiga et al: "Chiroptical properties of stereoisomeric conjugated oximes", Tetrahedron: Asymmetry, 2(5), 381-7 (English) 1991, see CASRN 135129-00-9	1-3,18,23, 33,42,44,46, 48,54,55,64, 69,71,79,88, 93,97,98,102
X	STEROIDS, Volume 48, 1986, Edward J. Parish et al, "Synthesis of 3 beta-Hydroxy-5 alpha-Cholest-8-En-7-one and 3 beta-Hydroxy-5 alpha-Cholest-8-En-11-One: Evaluation as Potential Hypocholesterolemic Agents", page 407 - page 418, see compounds I,II,VI	1-3,17,23, 33,42,44, 46-48,64,69, 71,79,88, 93, 97,98,102, 120-121

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 Sept 1996	27 -09- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00273

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1983:422756, Anastasia, Mario et al: "A new route to steroid ring-C aromatization from 7-oxygenated steroids", J. Chem.Soc., Perkin Trans. 1(3),587-90 (English) 1983, see CASRN 69140-15-4, 63115-68-4	1-3,17,23, 41,44,46,47, 54-55,64,69, 71,79,88,93, 97,98,102,116
X	STN International, File CAPLUS, CAPLUS accession no. 1989:566883, Parish, Edward J. et al: "Studies of the oxysterol inhibition of tumor cell growth", Steroids, 53(3-5), 579-96 (English) 1989, see CASRN 62250-89-9	1-3,12,27, 42,44,46-47, 64,69,71,79, 88,93,97,98, 102,116,120-121
X	STN International, File CAPLUS, CAPLUS accession no. 1979:420894, Patterson, Donald G. et al: "Stereochemical course of the chemical and catalytic reduction of 11-oxo-5.alpha., 14 beta.-cholest-8-en-3.beta.-ol. Synthesis of 8.alpha., 9.alpha.,14 beta.-,8.alpha.,9 beta., 14 beta.-, and 8 beta., 9 alpha., 14.beta.-steroids", J.Org.Chem., 44(11), 1866-71(English) 1979, see CASRN 69454-76-8, 69454-77-9, 62279-64-5	1-3,12,25, 27,33,42,44, 46,47,64,69, 71,79, 88,93, 97-98,102,116
P,X	WO 9600235 A1 (NOVO NORDISK A/S), 4 January 1996 (04.01.96)	1-121

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK96/00273

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 122-127
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claims Nos.: 1-121
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
A full evaluation of the state of the art has not been made for the claims 1-121, because the formulation of the claims is so complicated with a long list of cascading substituents. For this reason the search has been limited to the examples.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

International application No.
PCT/DK 96/00273

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9600235	04/01/96	AU-A- 2734395	19/01/96
		IL-D- 114294	00/00/00

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(74) Common Representative: BASF AKTIENGESELLSCHAFT; D–67056 Ludwigshafen (DE).

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Published
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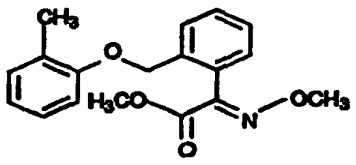
(54) Title: FUNGICIDAL MIXTURES



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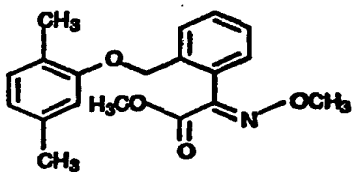

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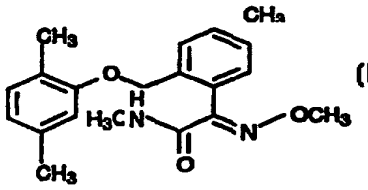

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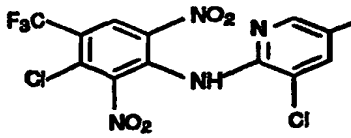

(II)

(57) Abstract

Fungicidal mixtures, comprising a) a phenyl–benzylether of formula (I.a), (I.b) or (I.c) and b) a dinitroaniline of formula (II) in a synergistically active amount.

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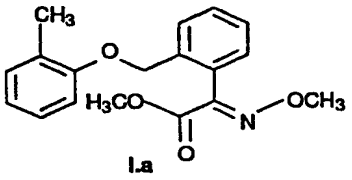
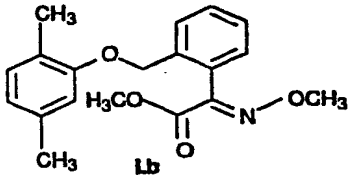
Fungicidal mixtures

The present invention relates to a fungicidal mixture which comprises

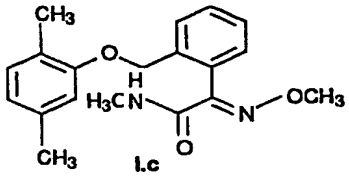
a) a phenyl-benzylether of the formula I.a, Ib or I.c,



I.a



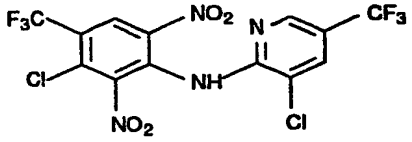
I.b



I.c

and

b) a dinitroaniline of the formula II



in a synergistically active amount.

Moreover, the invention relates to methods of controlling harmful fungi with mixtures of the compounds I (I.a, I.b and I.c) and II and to the use of the compound I and the compound II for the preparation of such mixtures.

The compounds of the formula I, their preparation and their action against harmful fungi have been disclosed in the literature (EP-A 253 213; EP-A 254 426; EP-A 398 692; EP-A 477 631).

The compound II (*CAS RN: 79622—59—6*, common name: fluazinam), its preparation and its action against harmful fungi have also been disclosed.

It was an object of the present invention to provide mixtures which have an improved activity gainst harmful fungi combined with a reduced total amount of active ingredients applied (synergistic mixtures) with a view to reducing the rates of applica-

tion and to improving the spectrum of action of the known compounds.

Accordingly, we have found that this object is achieved by the mixture defined at the outset. Moreover, we have found that better control of the harmful fungi is possible by applying the compound I and the compound II simultaneously together or separately or by applying the compound I and the compound II in succession than when the individual compounds are used.

Due to the basic character, the compound II is capable of forming adducts or salts with inorganic or organic acids or with metal ions.

Examples of inorganic acids are hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid and hydroiodic acid, sulfuric acid, phosphoric acid and nitric acid.

Suitable organic acids are, for example, formic acid, carbonic acid and alkanoic acids such as acetic acid, trifluoroacetic acid, trichloroacetic acid and propionic acid, and also glycolic acid, thiocyanic acid, lactic acid, succinic acid, citric acid, benzoic acid, cinnamic acid, oxalic acid, alkylsulfonic acids (sulfonic acids having straight-chain or branched alkyl radicals having from 1 to 20 carbon atoms), arylsulfonic acids or —disulfonic acids (aromatic radicals such as phenyl and naphthyl which have attached to them one or two sulfo groups), alkylphosphonic acids (phosphonic acids having straight-chain or branched alkyl radicals of from 1 to 20 carbon atoms), arylphosphonic acids or —diphosphonic acids (aromatic radicals such as phenyl and naphthyl which have attached to them one or two phosphoric acid radicals), it being possible for the alkyl or aryl radicals to have attached to them further substituents, eg. p—toluenesulfonic acid, salicylic acid, p—aminosalicylic acid, 2—phenoxybenzoic acid, 2—acetoxybenzoic acid etc.

Suitable metal ions are, in particular, the ions of the elements of the second main group, in particular calcium and magnesium, and of the third and fourth main group, in particular aluminum, tin and lead, and of the first to eighth sub—group, in particular chromium, manganese, iron, cobalt, nickel, copper, zinc and others. Especially preferred are the metal ions of the elements of the sub—groups of the fourth period. The metals can in this case be in the various valences which they can assume.

When preparing the mixtures, it is preferred to employ the pure active ingredients I and II, with which further active ingredients against harmful fungi or other pests such as insects, arachnids or nematodes, or else herbicidal or growth-regulating active ingredients or fertilizers can be admixed, if so desired.

The mixtures of the compounds I and II, or the simultaneous joint or separate use of the compounds I and II, are distinguished by an outstanding activity against a broad spectrum of phytopathogenic fungi, in particular from the classes of the Ascomycetes, Deuteromycetes, Phycomycetes and Basidiomycetes. Some of them act systemically and can therefore be employed as foliar— and soil—acting fungicides.

They are especially important for controlling a large number of fungi in a variety of crop plants such as cotton, vegetable species (eg. cucumbers, beans and curcubits), barley, grass, oats, coffee, maize, fruit species, rice, rye, soybeans, grapevine, wheat, ornamentals, sugar cane, and a variety of seeds.

They are particularly suitable for controlling the following phytopathogenic fungi: Erysiphe graminis (powdery mildew) on cereals, Erysiphe cichoracearum and Sphaerotheca fuliginea on curcubits, Podosphaera leucotricha on apples, Uncinula necator on grapevines, Puccinia species on cereals, Rhizoctonia species on cotton, rice and turf, rice and lawn, Ustilago species on cereals and sugar cane, Venturia inaequalis (scab) on apples, Helminthosporium species on cereals and turf, Septoria nodorum on wheat, Botrytis cinerea (gray mold) on strawberries, vegetables, ornamentals and grapevines, Sclerotina species in rape and turf, Cercospora arachidicola on peanuts, Pseudocercosporella herpotrichoides on wheat and barley, Pyricularia oryzae on rice, Phytophthora infestans on potatoes and tomatoes, Pythium species in ornamentals, vegetables and turf, Pseudoperonospora species on cucurbits and hops, Plasmopara viticola on grapevines, Alternaria species on vegetables and fruit, and Fusarium and Verticillium species.

Furthermore, they can be used in the protection of materials (eg. in the protection of wood), for example against Paecilomyces variotii.

The compounds I and II can be applied simultaneously together or separately or in succession, the sequence, in the case of separate application, generally not having any effect on the result of the control measures.

The compounds I and II are normally used in a weight ratio of from 20:1 to 0.1:2, preferably 10:1 to 1:1, in particular 5:1 to 0.2:1 (II:I).

The application rates of the mixtures according to the invention are, in the case of the compounds I, from 0.005 to 0.5 kg/ha, preferably 0.01 to 0.5 kg/ha, in particular 0.01 to 0.3 kg/ha, depending on the nature of the desired effect.

Correspondingly, in the case of the compound II, the application rates are from 0.1 to 10 kg/ha, preferably 0.2 to 5 kg/ha, in particular 0.3 to 3 kg/ha.

For seed treatment, the application rates of the mixture are generally from 0.001 to 100 g/kg seed, preferably 0.01 to 50 g/kg, in particular 0.01 to 10 g/kg.

If phytopathogenic harmful fungi are to be controlled, the separate or joint application of the compounds I and II or of the mixtures of the compounds I and II is effected by spraying or dusting the seeds, the plants or the soils before or after sowing of the plants, or before or after plant emergence.

The fungicidal synergistic mixtures according to the invention, or the compounds I and II, can be formulated for example in the form of ready-to-spray solutions, powders and suspensions or in the form of highly concentrated aqueous, oily or other suspensions, dispersions, emulsions, oil dispersions, pastes, dusts, materials for spreading or granules, and applied by spraying, atomizing, dusting, spreading or pouring. The use form depends on the intended purpose; in any case, it should guarantee as fine and uniform as possible a distribution of the mixture according to the invention.

The formulations are prepared in a manner known per se, eg. by adding solvents and/or carriers. It is usual to admix inert additives, such as emulsifiers or dispersants, with the formulations.

Suitable surfactants are the alkali metal salts, alkaline earth metal salts and ammonium salts of aromatic sulfonic acids, eg. ligno—, phenol—, naphthalene— and dibutylnaphthalenesulfonic acid, and of fatty acids, of alkyl— and alkylarylsulfonates, of alkyl, lauryl ether and fatty alcohol sulfates, and salts of sulfated hexa—, hepta— and octadecanols or fatty alcohol glycol ethers, condensates of sulfonated naphthalene and its derivati-

ves with formaldehyde, condensates of naphthalene, or of the naphthalenesulfonic acids, with phenol and formaldehyde, polyoxyethylene octylphenyl ether, ethoxylated isooctyl—, octyl— or nonylphenol, alkylphenyl polyglycol ethers or tributylphenyl polyglycol ether, alkylaryl polyether alcohols, isotridecyl alcohol, fatty alcohol/ethylene oxide condensates, ethoxylated castor oil, polyoxyethylene alkyl ethers or polyoxypropylene, lauryl alcohol polyglycol ether acetate, sorbitol esters, lignin-sulfite waste liquors or methylcellulose.

Powders, materials for spreading and dusts can be prepared by mixing or jointly grinding the compounds I or II or the mixture of the compounds I and II with a solid carrier.

Granules (eg. coated granules, impregnated granules or homogeneous granules) are normally prepared by binding the active ingredient, or active ingredients, to a solid carrier.

Fillers or solid carriers are, for example, mineral earths such as silicas, silica gels, silicates, talc, kaolin, limestone, lime, chalk, bole, loess, clay, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, and fertilizers such as ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders or other solid carriers.

The formulations generally comprise from 0.1 to 95% by weight, preferably 0.5 to 90% by weight, of one of the compounds I or II, or of the mixture of the compounds I and II. The active ingredients are employed in a purity of from 90% to 100%, preferably 95% to 100% (according to NMR or HPLC spectrum).

The compounds I or II, or the mixtures, or the corresponding formulations, are applied by treating the harmful fungi or the plants, seeds, soils, areas, materials or spaces to be kept free from them with a fungicidally active amount of the mixture, or of the compounds I and II in the case of separate application. Application can be effected before or after infection by the harmful fungi.

Examples of the synergistic action of the mixtures according to the invention against harmful fungi

Activity against Botrytis cinerea in pepper seedlings

Seedlings of pepper of the variety "Neusiedler Ideal Elite", after development of 4-5 leaves were sprayed to runoff with an aqueous suspension prepared from a master solution containing 10 wt.% of active ingredient or mixture of active ingredients, 63 wt.% cyclohexanone and 27 wt.% emulsifier. One day later the sprayed-on layer had dried and the leaves were inoculated with a spore suspension of Botrytis cinerea containing 1.7×10^6 spores per ml (2 wt.% bio malt solution). The inoculated plants were then cultivated in chambers with high humidity for five days at from 18 to 22 °C.

The leaf area under fungus attack was then assessed visually in percent. These figures were then converted into degrees of control. The degree of control in the untreated plants was set at 0. The degree of control when 0% of the leaf area was attacked was set at 100.

The degree of control (W) was calculated in accordance with the Abbott formula as follows:

Abbott formula: $W = (1 - \alpha) \bullet 100 : \beta$

α fungus attack of treated plants [%] and
β fungus attack of untreated control plants [%]

The expected degrees of action of the active ingredient compositions were determined in accordance with the Colby formula and compared with the degrees of action observed.

The values for the fungicidal action varied between the individual experiments because the plants in the individual experiments exhibited varying degrees of attack; for this reason, only the results within the same experiment can be compared with each other.

Colby formula: $E = x + y - (x \bullet y : 100)$

E = expected degree of action, expressed in % of the untreated control, when active ingredients A and B are applied together, the concentration of A being [a] and the concentration of B being [b]

x = degree of action of ingredient A, expressed in % of the untreated control, when a concentration [a] of the active ingredient A is applied

y = degree of action of ingredient B, expressed in % of the untreated control, when a concentration [b] of the active ingredient B is applied

As a general rule the comparison of the expected degree of action (E according to the Colby formula) with the degree of action found shows whether the effect is synergistic or not, the correlation being as follows:

degree of action found > (E) => synergism
degree of action found ≤ (E) => no synergism

The test results are listed in the following tables:

Table 1

Example	Compound	Appln. Rate [ppm]	Degree of Control (Abbott)
1V	None	(100 % attack)	0
2V	Compound Ia	3.1	10
3V	Compound Ia	0.8	0
4V	Compound Ic	3.1	10
5V	Compound Ic	0.8	0
6V	Compound II	3.1	10
7V	Compound II	0.8	0

The results achieved with compositions in accordance with the instant invention are listed in the following table.

Table 2

Example	Mixture	Degree of action (observed)	Degree of action (calculated)
8	3.1 ppm Ia + 3.1 ppm II	97	19
9	0.8 ppm Ia + 0.8 ppm II	95	0

Example	Mixture	Degree of action (observed)	Degree of action (calculated)
10	3.1 ppm Ic + 3.1 ppm II	100	19
11	0.8 ppm Ic + 0.8 ppm II	75	0

These test results clearly demonstrate that compositions comprising compounds Ia or Ic and compound II exhibit synergism at different application rates and in different ratios.

Activity against Botrytis cinerea on pepper fruits

Disks of green peppers were sprayed to runoff with an aqueous suspension prepared from a master solution containing 10 wt.% of active ingredient or mixture of active ingredients, 63 wt.% cyclohexanone and 27 wt.% emulsifier. 2 hours after the sprayed-on layer had dried the disks were infected with a spore suspension of Botrytis cinerea containing 1.7 x 10^6 spores per ml (2 wt.% bio malt solution). The infected fruit disks were then cultivated in chambers with high humidity for four days at 18 °C.

The fruit disk area under fungus attack was then assessed visually in percent. These figures were then converted into degrees of control. The degree of control in the untreated disks was set at 0. The degree of action when 0% of the fruit disk area was attacked was set at 100. The degree of control and degree of action were determined as in Examples 1 to 11.

The test results are listed in the following tables:

Table 3:

Example	Compound	Appln. Rate [ppm]	Degree of Control (Abbott)
12V	None	(95 % attack)	0
13V	Compound Ia	3.1	26
14V	Compound Ia	0.8	16
15V	Compound Ic	3.1	16
16V	Compound Ic	0.8	5

Example	Compound	Appln. Rate [ppm]	Degree of Control (Abbott)
17V	Compound II	3.1	5
18V	Compound II	0.8	0

The results achieved with compositions in accordance with the instant invention are listed in the following table.

Table 4

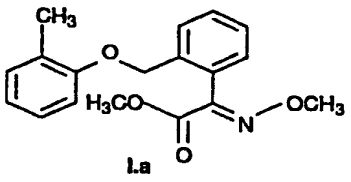
Example	Mixture	Degree of action (observed)	Degree of action (calculated)
19	3.1 ppm Ia + 3.1 ppm II	68	30
20	0.8 ppm Ia + 0.8 ppm II	45	16
21	3.1 ppm Ic + 3.1 ppm II	47	20
22	0.8 ppm Ic + 0.8 ppm II	35	5

These test results clearly demonstrate that compositions comprising compounds Ia or Ic and compound II exhibit synergism at different application rates and in different ratios.

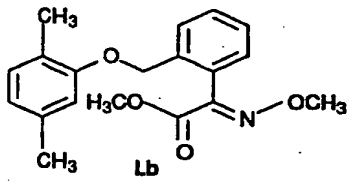
We claim:

1. A fungicidal mixture comprising

a) a phenyl-benzylether of the formula I.a, I.b or I.c,



I.a



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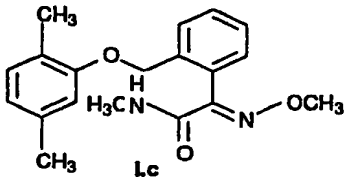
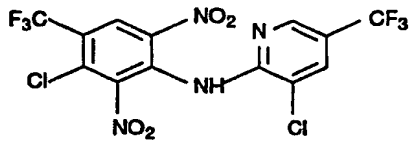


I.c

and

b) a dinitroaniline of the formula II



in a synergistically active amount.

2. A fungicidal mixture as claimed in claim 1 wherein the weight ratio of the compound II to the compound I is 20:1 to 0.1:2.

3. A method of controlling harmful fungi, which comprises treating the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them with a compound of the formula I as set forth in claim 1 and the compound of the formula II as set forth in claim 1.

4. A method as claimed in claim 3, wherein a compound I as set forth in claim 1 and the compound II as set forth in claim 1 are applied simultaneously together or separately or in succession.

5. A method as claimed in claim 3, wherein the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them are treated with

from 0.005 to 0.5 kg/ha of a compound I as set forth in claim 1.

6. A method as claimed in claim 3, wherein the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them are treated with from 0.1 to 10 kg/ha of the compound II as set forth in claim 1.

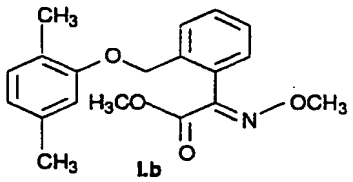
AMENDED CLAIMS

[received by the International Bureau on 17 November 1998 (17.11.98); original claim 1 amended; remaining claims unchanged (2 pages)]

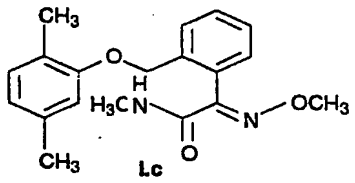
We claim:

1. A fungicidal mixture comprising

a) a phenyl-benzylether of the formula I.b or I.c,



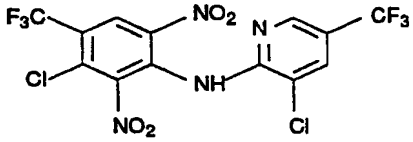
Lb



Lc

and

b) a dinitroaniline of the formula II



in a synergistically active amount.

2. A fungicidal mixture as claimed in claim 1 wherein the weight ratio of the compound II to the compound I is 20:1 to 0.1:2.

3. A method of controlling harmful fungi, which comprises treating the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them with a compound of the formula I as set forth in claim 1 and the compound of the formula II as set forth in claim 1.

4. A method as claimed in claim 3, wherein a compound I as set forth in claim 1 and the compound II as set forth in claim 1 are applied simultaneously together or separately or in succession.

5. A method as claimed in claim 3, wherein the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them are treated with from 0.005 to 0.5 kg/ha of a compound I as set forth in claim 1.

6. A method as claimed in claim 3, wherein the harmful fungi, their environment, or the plants, seeds, soils, areas, materials or spaces to be kept free from them are treated with from 0.1 to 10 kg/ha of the compound II as set forth in claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 98/02947

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01N43/40 //(A01N43/40,37:50)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 741 970 A (SUMITOMO CHEMICAL CO) 13 November 1996	1-6
Y	see page 2 see page 3, compound Ia and page 4, compound Ie see page 5, line 31 - line 34 se the for formulation examples 31-36 and test example 11	1-6
Y	WO 97 15189 A (BASF AG ;HAMPEL MANFRED (DE); SCHELBERGER KLAUS (DE); LORENZ GISEL) 1 May 1997 see page 1, line 4 - line 40	1-6
P,A	WO 97 40687 A (BASF AG ;MUELLER BERND (DE); SAUTER HUBERT (DE); AMMERMANN EBERHAR) 6 November 1997 see page 1 - page 2, line 31	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1998	26/10/1998

Name and mailing address of the ISA	Authorized officer
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